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CLINICAL TRIAL REPORT

A phase I clinical trial of low-dose interferon-α-2A, thalidomide plus gemcitabine and capecitabine for patients with progressive metastatic renal cell carcinoma

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Abstract
Background We have conducted a phase I trial to determine the maximum tolerated dose of gemcitabine in combination with interferon, thalidomide and capecitabine.
Methods Patients received oral capecitabine 1,000 mg/m^2 per day, divided in 2 daily doses, 2 weeks on, 1 week off; subcutaneous interferon-α 1 mIU twice a day without an interruption; daily oral thalidomide 200 mg/day for the first 7 days, then escalated to 400 mg/day without an interruption. Gemcitabine was given by intravenous administration over 30 min on day 1, week 1 and day 8, week 2. Initial dose level of gemcitabine was 400 mg/m^2. The dose of gemcitabine was the phase I variable. One cycle was 3 weeks.
Results and discussion We treated 12 patients, 6 patients were entered at a dose level of 0 (gemcitabine 400 mg/m^2) and 6 patients entered at a dose level-1 (gemcitabine 200 mg/m^2). Eight of 12 patients completed at least 12 weeks of therapy. Three partial responses and two stable disease were observed. The remaining patients had progressive disease. Non-hematologic toxicity was either grade 1 or 2. Hematologic toxicity at dose level 0 consisted of 3 patients with grade 3/4 neutropenia, and 1 patient with grade 3 thrombocytopenia. At dose level-1 grade 1/2 neutropenia was observed.
Conclusions The completion of our phase I experience determined our maximum tolerated dose to be dose level-1. The phase II trial is currently being proposed for patients with rapidly growing clear cell, other histologies that may contain sarcomatoid elements or collecting duct tumor.

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Introduction

Renal cell cancer (RCC) affects approximately 51,190 people annually in the United States with an estimated 12,890 deaths [1]. Although localized RCC may be cured by surgery, patients with metastatic RCC (MRCC) are incurable. Metastatic disease is present in approximately 30% of RCC patients at the time of diagnosis, and another 30–40% of patients with early stage disease relapse with metastatic disease following nephrectomy. Immunotherapy has been the primary systemic treatment approach. High-dose interleukin-2 (IL-2) has been the only FDA approved drug that has led to occasional complete responses. However, only a minority of patients were eligible to receive high dose IL-2 therapy. Although outpatient interferon-α at various dose schedules led to improvement in survival, the benefit still was minimal. Recently, anti-targeted agents, oral tyrosine kinase inhibitors, inhibiting the vascular endothelial growth factor receptor and the platelet derived growth factor receptor, have been approved by the FDA for cytokine failures. Sunitinib produces high rates of objective response, while Sorafenib improved time to progression in a placebo controlled phase 3 trial [2–4]. However, these therapies remain palliative, and the data suggests that the majority of patients will eventually progress. Thus, there is an ongoing need to develop treatment regimens for patients with progressive MRCC.

To date, attempts to treat locally advanced MRCC with chemotherapy have been unsuccessful. Response rates of 4–18% are not exceeded for any single agent or combination regimen. Interferon-α has undergone extensive evaluation as

treatment for metastatic RCC. Although response rates are 5–15%, most of these are partial and short lived [5]. The administration of high dose bolus IL-2 has produced modest stable responses in a small percentage of patients (19% overall response rate). Significant toxicities can occur with this regimen, and it is applicable to a limited number of patients [5, 6].

Chemotherapeutic agents reported to have antitumor effect include the fluoropyrimidines, floxuridine (FuDR) and 5-fluorouracil (5-FU). These agents are often used in combination with interferon given the modulation that is known to occur. Capecitabine is a new oral fluoropyrimidine carbonate that was designed to be selectively converted to 5-FU by sequential triple enzyme pathway [7]. The last tumor selected reaction is mediated by the tumor-associated angiogenic factor, thymidine phosphorylase. Thymidine phosphorylase levels are increased in several types of malignant tumors compared to the adjacent non-neoplastic tissue. Over expression of thymidine phosphorylase occurs in RCC. It is hoped that capecitabine may offer an advantage in RCC along with an easier administration schedule and perhaps toxicity profile. With respect to toxicity, there are differences in the toxicity profile between capecitabine and 5-FU. The treatment-related adverse events most common with capecitabine are: diarrhea, nausea, hand/foot syndrome, vomiting, and fatigue. The most frequent laboratory abnormalities are liver function studies predominately an elevated bilirubin, generally not associated with elevated alkaline phosphatases or hepatic transaminases. Myelosuppression is rarely reported. The lack of stomatitis is a dose limiting toxicity of capecitabine is potentially very important given that it is often a significant problem in patients previously treated with combined immunotherapy and 5-FU.

Gemcitabine is a pyrimidine nucleoside antimetabolite that, once converted to diflurodeoxycytidine triphosphate, inhibits DNA synthesis by inhibition of DNA polymerase and direct incorporation in DNA leading to premature termination of DNA chain elongation. Gemcitabine has significant clinical activity in multiple solid tumors. In breast cancer xenograft models, there appears to be synergistic effects when combining with capecitibine.

Chronic, low-dose interferon-α (IFN-α) behaves as an angiogenesis inhibitor [8] Angiogenesis has been well established in RCC. RCC patients with high levels of angiogenic factor basic fibroblastic growth factor (bFGF) have a poor survival than patients with lower bFGF levels, suggesting that increased angiogenesis due to bFGF production may lead to increased metastatic potential and consequently decrease survival [9, 10] IFN-α has been shown to ameliorate this overproduction to bFGF.

The immunomodulatory drug thalidomide (Thalidomid®) has been investigated in MRCC as a single agent with some promising results [11–15]. Thalidomide has induced marked and durable responses in the patient population [11], with some activity evident in heavily treated patients [13]. Thalidomide has also been studied in combination regimens incorporating interleukin-2 (IL-2), Gemcitabine plus 5-fluorouracil and/or IFN-α in MRCC, with response rates ranging from 14 to 42% and adverse effects generally tolerable [16–18]

We recently reported the antitumor activity of combined interferon-α, capecitabine, and thalidomide in MRCC [6]. While there were no complete responses observed, 20% partial response rate is particularly notable because this patient population had advanced disease, poor performance status and prior treatment. Although 5 patients with stable disease were not determined as treatment successes, their median overall survival rate of 14 months was notably higher than that in patients with progressive disease (1 month). These results suggested that further study of various combinations of interferon-α, capecitabine, and thalidomide was warranted in previously treated MRCC patients.

Based upon these reports, we initiated a phase I study of interferon-α, thalidomide and capecitabine with variable dose levels of gemcitabine in previously treated patients with MRCC.

Patients and methods

Patients

Patients with all histologic RCC subtypes, including those with components of sarcomatoid differentiation, were eligible for enrollment. Eligibility criteria included: any prior immunotherapy or chemotherapy regimen; Zubrod performance status (ZPS) $\leq$2; expected survival of $\geq$12 weeks; full recovery from previous surgery or radiation therapy, adequate liver, renal, and hematologic function. Due to thalidomide's known teratogenic effects, it was also necessary for patients to agree to practice approved methods of birth control, if appropriate.

Exclusion criteria included: concurrent radiation therapy or surgery; active brain metastasis; unstable medical condition (e.g., uncontrolled diabetes, angina, or hypertension); serious infection; cardiac or pulmonary dysfunction (including unstable chronic congestive heart failure, uncontrolled arrhythmia; unstable coagulation disorder, or recent myocardial infarction); and previous therapy was greater than 4 weeks from time of study entry with appropriate recovery from previous toxicity. Written informed consent was obtained from all patients, and approval from our institutional review board was obtained.

Pretreatment examinations

Pretreatment evaluations to determine eligibility consisted of, a medical history and physical examination with ZPS; vital signs; cardiac profile (ECG and echocardiogram); hematology (CBC with differential, platelet count); coagulation (PTT, PT, and INR); and chemistry profile (total protein, albumin, BUN, creatinine, sodium, potassium, chloride, CO_2 content, bilirubin, SGPT, SGOT, alkaline phosphatase, and lactate dehydrogenase); and urinalysis. Imaging consisted of: CT scan of the chest, abdomen, and pelvis; MRI of the brain; and bone scan performed within 4 weeks of initial study treatment. Female patients of childbearing potential were subject to a βHCG pregnancy test within 7 days before treatment initiation.

Phase I treatment regimen

Oral thalidomide was administered daily at bedtime. The initial dose of thalidomide was 200 mg/day administered for 7 days. The thalidomide dose was increased by a 200 mg increment on day 8 to achieve the assigned dose. Capecitabine 1,000 mg/m^2/day orally divided in 2 daily doses administered 2 weeks on, 1 week off. Capecitabine was taken with water and not fruit juices. Antacids were avoided, as they may interfere with the dilution and absorption of capecitabine. Interferon-α-2α 1 mIU given subcutaneously administered twice a day, daily without an interruption. In the absence of dose-limiting toxicities (DLT), grade 3 or 4 major organ toxicities, patients were treated with gemcitabine with an initial dose of 400 mg/m^2 day 1, week 1 and day 8, week 2. Table 1 describes the dose-ranging phase. Treatment was administered on an outpatient basis, with a treatment course defined as 3 weeks.

Definition of dose limiting toxicity and maximum tolerated dose

Dose limited toxicity was assessed during the first cycle of chemotherapy and defined as any non-hematologic toxicity of grade 3/4, thrombocytopenia, or neutropenia. Three patients were enrolled at each dose level, and additional patients were enrolled until $\geq$3 patients were evaluable for DLT. Dose escalation would proceed if no patient experienced a DLT. If a DLT attributable to the study drugs was observed in one of the first three patients, three more patients were enrolled at the same dose level. If $\geq$33% of the patients at any dose level experienced a DLT, or if any patient experienced multiple DLTs, dose escalation was not permitted. Before patients were treated at a higher dose level, all patients at the previous dose level are observed for 3 weeks. No intra-patient dose escalation was permitted. The maximum tolerated dose (MTD) was defined as the highest dose tested at which <33% of patients experienced DLT attributable to the study drugs, when $\geq$6 patients were treated at that dose and were evaluable for DLT.

Patient assessments

Weekly evaluations examined hematology and limited chemistry profile (creatinine, BUN, sodium, potassium, chloride, CO_2 content, bilirubin, SGPT, SGOT, alkaline phosphatase). Hematology profile was performed twice a week if the absolute granulocyte count was <1,500 or the platelet count was <100,000, until recovery. Every 3 weeks an evaluation included interim history, physical examination, including ZPS. Hematologic toxicity was assessed every week. Non-hematologic toxicity was assessed every 3 weeks. Toxicities were evaluated according to the National Cancer Institute, common toxicity criteria (NCI-CTC) version 2.0.

The first evaluation of tumor response to therapy was assessed after 4 cycles of therapy (12 weeks) using imaging studies. Patients determined to be stable or responding to therapy (RECIST criteria) were then assessed every 6–12 weeks (Table 2).

Results

Toxicity

Twelve patients were enrolled between July 2003 and March 2004 (Table 1). All patients received at least 1 course (3 weeks) of the combination treatment and were accessible for toxicity. DLT was observed at starting dose level 0 (gemcitabine, 400 mg/m^2). Three of six patients experienced grade 3/4 neutropenia and one patient with grade 3 thrombocytopenia. As per study design, dose

Table 1 Study design

Dose level	Number of patients	Interferon dosage	Thalidomide dosage (mg)	Capecitabine dosage (days 1–14, weeks 1 and 2) (mg/m^2)	Gemcitabine dose levels (day 1, week 1 and day 8, week 2)
−1	6	1 mIu bid	200–400	1,000	200
0	6	1 mIu bid	200–400	1,000	400

Table 2 Patient characteristics ($N = 12$)

Characteristic	Number of patients
Gender	
Male	9
Female	3
Race	
Caucasian	11
African American	1
Histology	
Clear-cell	5
Papillary	2
Collecting duct	5
Sarcomatoid elements	4
Fuhrman's grade	
Grade 2	1
Grade 3	5
Grade 4	6
Previous systemic therapy	
0	1
1	5
2	4
>2	2
Number of sites of metastatic disease	
1	0
2	2
≥3	10

reduction to the next lower dose level-1 (gemcitabine, 200 mg/m^2) occurred. At this dose level only grade 1 or 2 neutropenia was observed.

In all patients, grade 1 and 2 non-hematologic toxicity consisted of hand/foot syndrome, fatigue, nausea, emesis, constipation, diarrhea, and paresthesia. In addition, grade 2 anemia was observed. Two patients experienced associated with chronic administration of therapy deep venous thrombosis

Antitumor effects

Among 12 evaluable patients, 3 partial responses were observed for 3, 4, and 7 months respectively. Two patients had stable disease for 3 and 4 months, respectively. There were no complete responses.

Radiographic responses were confirmed by an independent radiologist from the Methodist Hospital, Department of Radiology.

Discussion

Treatment of patients with aggressive renal cell tumors who have undergone multiple previous therapies remains a therapeutic challenge. Attempts to increase antitumor activity by combining biologic agents and chemotherapy agents may offer new hope for the treatment of these aggressive cancers. This phase 1 clinical trial investigated gemcitabine administered once a week for two consecutive weeks in combination with interferon-α, thalidomide and capecitabine, which has been previously reported [6]. The purpose of this trial was to determine whether this combination regimen is feasible and safe in patients with MRCC in order to establish a phase 2 trial to determine antitumor activity.

The rationale for combining gemcitabine and capecitabine in patients with solid tumors is based on preclinical and phase 1 clinical data. Because preclinical data suggests synergism for this combination of chemotherapeutic agents, it seems reasonable to combine these agents in combination with known biologic active drugs such as interferon and thalidomide.

In our previous study combining interferon-α, capecitabine and thalidomide in progressive MRCC patients, the 20% partial response rate was reported, and an additional 30% had stable disease [19]. The median overall survival for those patients who received a partial response was 22 months, and for patients who achieved stable disease the median overall survival rate was 14 months. This was compared to those individuals with progressive disease who had a median overall survival of 1 month. Despite the inability to increase the dose of gemcitabine, three patients achieved a durable partial response who were previously treated with two or more regimens, and two patients previously treated achieved stable disease for 3–4 months. The responses observed were in patients with expotentially growing RCC patients (2), one patient with papillary and two patients with collecting duct tumor. One patient with predominant sarcomatoid elements had a significant partial response.

This study demonstrates that adding gemcitabine to the three-drug regimen was not successful. The reasons for this statement are the following: First, the dose of capecitabine was reduced to 1,000 mg/m^2, as opposed to the trial reported earlier where the initial dose was 1,900 mg/m^2. Second, the dose of gemcitabine that could be achieved was extremely low. This was a result of unacceptable toxicity at dose level 0.

Despite the limited number of patients, responses were observed. No blood or tissue samples were obtained in the current study, precluding further characterization of the combination. These results suggest combination of interferon-α, thalidomide, plus capecitabine with Gemcitabine add additional toxicity and have a similar response rate to the combination previously reported interferon-α, thalidomide plus capecitabine without the Gemcitabine. Further investigation on this combination without the Gemcitabine is recommended as a viable treatment option.

Further investigation on this combination is recommended as a viable treatment option for patients with rapidly growing clear cell cancer or uncommon pathology such as collecting duct or those with a predominant sarcomatoid element. An additional area of research given emerging preclinical and clinical data, the potentiation of chemotherapy with vascular endothelial growth factor pathway directed agents.

In summary, the biologic chemotherapy combination of interferon-α, thalidomide plus capecitabine and gemcitabine needs further scheduled development and identification of the specific population that would most likely benefit from this therapy regimen.

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